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A NEW ENTRY TO THE SYNTHESIS OF (±)-*β*-LYSINE

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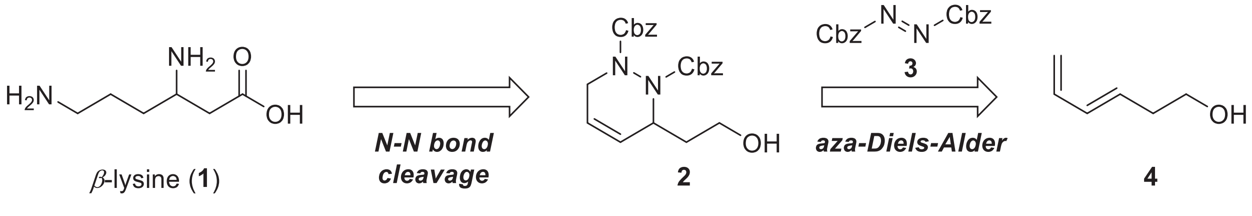
Abstract – A 3-step synthesis of (±)-*β*-lysine from ethyl sorbate featuring the aza-Diels-Alder reaction is described.

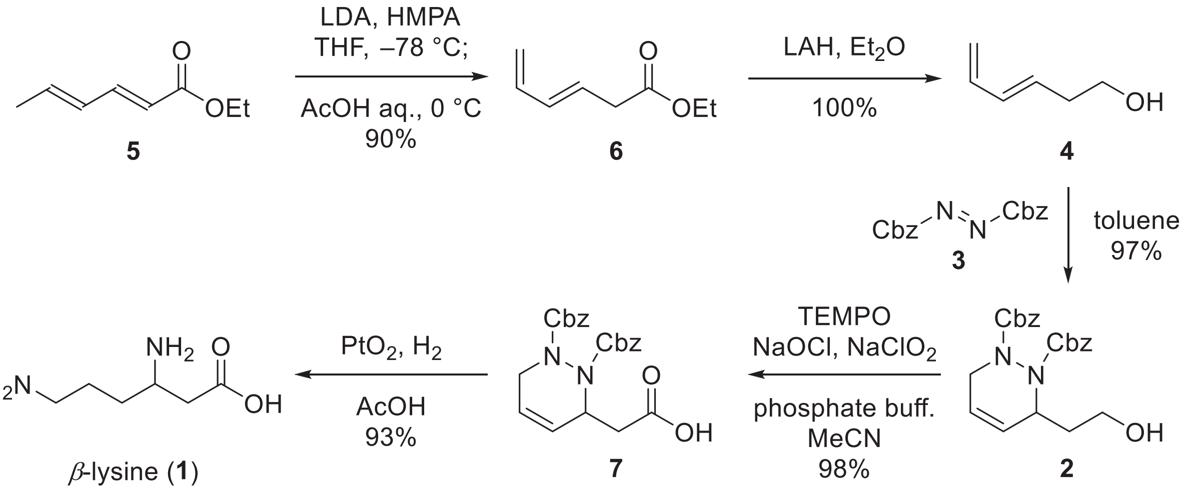
β-Amino acids are important structural motifs in bioactive compounds,[1] and have attracted intense attention in peptidomimetics research[2] and the biosynthesis of natural products.[3] In the course of our biosynthetic studies on amino acid-derived natural products, we needed to prepare a large amount of (±)-*β*-lysine.[4] *β*-Lysine is structurally characterized by its 1,4-diamine moiety, and several racemic and asymmetric syntheses of *β*-lysine featuring [3+2] cycloaddition[5] or conjugate addition of a homochiral lithium amide[6] have been disclosed to date.[7] We were also interested in the uniquely functionalized structure of *β*-lysine with its two amino groups, and thus decided to develop a new synthetic route. Here, we report a synthesis of (±)-*β*-lysine (**1**) by using an aza-Diels-Alder reaction as the key step. The 3-step synthesis from the commercially available ethyl sorbate enabled us to prepare a sufficient amount of (±)-*β*-lysine for biosynthetic studies.

The synthetic plan is illustrated in Scheme 1. We envisioned that the 1,4-diamine moiety of *β*-lysine (**1**) would be constructed by the aza-Diels-Alder reaction of the readily available diene **4** and azodicarboxylate **3**.[8] The reductive cleavage of the N-N bond and adjustment of the oxidation state of the cycloadduct **2** would deliver *β*-lysine.



Scheme 1. The synthetic plan of (±)-*β*-lysine (**1**)

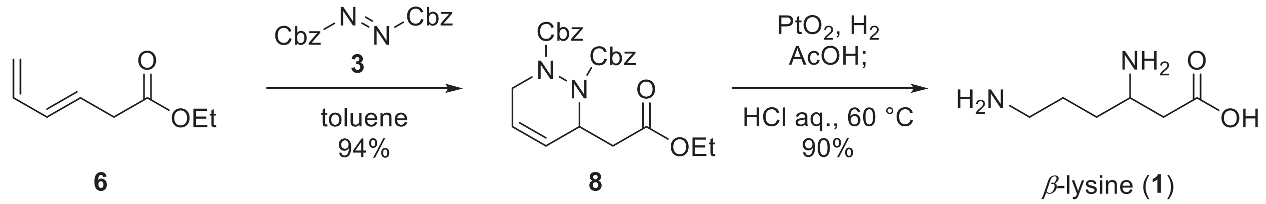
The synthesis commenced with the preparation of known alcohol **4** (Scheme 2).[9] Treatment of ethyl sorbate (**5**) with lithium diisopropylamide (LDA) followed by acidic work-up afforded diene **6**. To prevent the isomerization of **6** into the more stable **5**, compound **6** was immediately reduced with lithium aluminum hydride (LAH) to **4**. The aza-Diels-Alder reaction of **4** with dibenzyl azodicarboxylate (**3**) smoothly proceeded at ambient temperature, giving rise to **2**. After TEMPO oxidation of the hydroxy group of **2** to the carboxylic acid, the obtained **7** was converted into **1** in a single step. Specifically, by using AcOH as the solvent with Adams' catalyst[10] under H_2 atmosphere, the reduction of **7** induced the cleavage of the two Cbz groups and the N-N bond,[11] and simultaneously saturated the double bond, to furnish **1**.



Scheme 2. The synthesis of (±)-*β*-lysine (**1**)

We demonstrated that the aza-Diels-Alder reaction served as an effective method to construct the 1,4-diamino moiety of **1**. Most importantly, the aza-Diels-Alder reaction could be employed at ambient temperature without the use of any acids for improving the cycloaddition. The efficiency of this cycloaddition led us to next explore the use of unstable **6** as the diene instead of **4**.

Although the isomerization of **6** to **5** was concerning, the aza-Diels-Alder reaction of **6** and **3** proceeded without significant isomerization, providing **8** in 94% yield (Scheme 3). The reduction of **8** with Adams' catalyst and H_2 in AcOH was followed by hydrolysis of the ester by one-pot addition of aqueous HCl, giving rise to **1**. Overall, the 3-step synthetic route to **1** from **5** was established. All steps could be carried out on a gram-scale without any problematic manipulations.



Scheme 3. The improved synthesis of (±)-*β*-lysine (**1**)

In conclusion, we have established a practical synthetic route to (±)-*β*-lysine (**1**) utilizing the aza-Diels-Alder reaction of **6** and **3** as the key step for constructing the 1,4-diamino group. Not only the cycloaddition, but also the reduction of **8** with Adams' catalyst in AcOH realizing three transformations in a single step, contributed to the overall efficiency of the synthetic route. Studies on the biosynthesis of the natural product using (±)-*β*-lysine (**1**) are underway in our research group.

EXPERIMENTAL

General Methods: All reactions sensitive to air or moisture were carried out in dry solvents under argon atmosphere, unless otherwise noted. THF and Et_2O (dehydrated, stabilizer free) were purchased from Kanto Chemical Co., Inc. All other reagents were used as supplied. Analytical thin-layer chromatography (TLC) was performed using Merck TLC Silica Gel 60 F_{254} (0.25 mm). Flash chromatography was performed using 63–210 μm Silica Gel 60N (Kanto Chemical Co., Inc.). Infrared (IR) spectra were recorded as a thin film using PerkinElmer Spectrum 100 spectrometer. ^1H and ^{13}C NMR spectra were recorded on Bruker AVANCE NEO 500 spectrometer. Chemical shifts are reported in ppm on the δ scale relative to DMSO (δ = 2.50 for ^1H NMR), DMSO-d_6 (δ = 39.52 for ^{13}C NMR) or TMSP-d_4 sodium salt in D_2O (δ = 0 for ^1H and ^{13}C NMR) as internal references. Signal patterns are indicated as s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broaden peak. High resolution mass spectra were measured on Bruker micrOTOF (ESI-TOF) or Bruker compact (ESI-TOF).

Ethyl (*E*)-hexa-3,5-dienoate (6): *n*-BuLi (2.76 M in hexane, 23 mL, 64 mmol) was added to a solution of diisopropylamine (9.2 mL, 64 mmol) in THF (43 mL) at –78 °C. After warmed to 0 °C, the solution was stirred for 15 min. Then the solution was cooled to –78 °C. To the solution was added HMPA (23 mL), followed by a solution of ethyl sorbate (**5**) (5.35 mL, 35.7 mmol) in THF (14 mL). After stirred for 20 min at the same temperature, the reaction mixture was poured into aqueous AcOH (3.1 M, 100 mL) at 0 °C. The resultant mixture was extracted with hexane (100 mL ×3). The combined organic layer was washed with saturated aqueous $NaHCO_3$ (20 mL) and brine (20 mL), dried over Na_2SO_4 and concentrated to afford **6** (4.50 g, 32.1 mmol, 90%) as a colorless oil. The product was sufficiently pure, and used for the next reaction without further purifications. The compound data were identical with those reported previously.[9]

(*E*)-Hexa-3,5-dien-1-ol (4): A solution of ethyl (*E*)-hexa-3,5-dienoate (**6**) (4.50 g, 32.1 mmol) in Et_2O (8.0 mL) was added to a suspension of lithium aluminum hydride (1.49 g, 39.3 mmol) in Et_2O (23 mL) at 0 °C. After the reaction mixture was stirred for 4 h at room temperature, Et_2O (11 mL) and lithium aluminum hydride (750 mg, 19.8 mmol) were added. After the reaction mixture was stirred for 1 h at room temperature, Et_2O (11 mL) and saturated aqueous potassium sodium tartrate (50 mL) were added at 0 °C. After vigorously stirred for 15 h at room temperature, the resultant mixture was extracted with Et_2O (100 mL ×2). The combined organic layer was washed with brine (30 mL), dried over $MgSO_4$, and filtered through a pad of silica gel (20 g, Et_2O: 500 mL). The resultant solution was concentrated to afford **4** (6.08 g, 52 wt% mixture of Et_2O, 32.1 mmol, 100%). The compound data were identical with those reported previously.[9]

Dibenzyl 3-(2-hydroxyethyl)-3,6-dihydropyridazine-1,2-dicarboxylate (2): Dibenzyl azodicarboxylate (**3**) (1.7 M in CH_2Cl_2, 4.6 mL, 7.8 mmol) was added to a solution of (*E*)-hexa-3,5-dien-1-ol (**4**) (1.08 g, 52 wt% mixture of Et_2O, 5.72 mmol) in toluene (13 mL) at room temperature. After stirred for 22 h, the reaction mixture was concentrated and purified by flash column chromatography on silica gel (150 g, EtOAc/hexane 1/1 to 2/1) to afford **2** (2.19 g, 5.52 mmol, 97%) as a colorless oil: IR (neat) ν 3484, 2954, 1703, 1409, 1282, 1213, 1059, 750, 734, 695 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6, 373K) δ 1.56–1.77 (2H, m), 3.30–3.65 (2H, m), 3.65–3.93 (1H, m), 4.00–4.12 (1H, m), 4.26–4.35 (1H, m), 4.67–4.75 (1H, m), 5.00–5.30 (4H, m), 5.75–5.85 (1H, m), 5.85–5.94 (1H, m), 7.10–7.54 (10H, m). ^{13}C NMR (125 MHz, DMSO-d_6, 373K) δ 35.5, 42.0, 52.0, 57.4, 66.6, 66.8, 122.0, 126.7, 127.0, 127.3, 127.5, 127.77, 127.80, 135.7, 135.8, 154.1, 154.7. HRMS (ESI) calcd for $C_{22}H_{24}O_5N_2Na$ 419.1577 $[M+Na]^+$, found 419.1572.

2-(1,2-Bis((benzyloxy)carbonyl)-1,2,3,6-tetrahydropyridazin-3-yl)acetic acid (7): NaOCl (0.60 mL, 5% in H_2O, 0.40 mmol) was added to a mixture of **2** (1.54 g, 3.88 mmol), $NaClO_2$ (1.03 g, 11.4 mmol), and (2,2,6,6-tetramethylpiperidin-1-yl)oxyl (60.0 mg, 384 μmol) in phosphate buffer (pH 7, 12 mL) and MeCN (20 mL) at 0 °C. After stirred for 5 min, the reaction mixture was warmed to room temperature. After 3 h, aqueous HCl (1.0 M, 40 mL) was added at 0 °C. The resultant mixture was extracted with CH_2Cl_2 (30 mL ×2). The combined organic layer was washed with brine (10 mL), dried over $MgSO_4$, and concentrated to afford **7** (1.56 g, 3.80 mmol, 98%) as a colorless amorphous solid: IR (neat) ν 3110, 3035, 1706, 1406, 1272, 1213, 1064, 750, 734, 695 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6, 373K) δ 2.47 (1H, dd, *J* = 16.0, 7.2 Hz), 2.59 (1H, br dd, *J* = 16.0, 6.4 Hz), 3.76 (1H, br d, *J* = 17.0 Hz), 4.27–4.35 (1H, m), 4.93–5.00 (1H, m), 5.03–5.22 (4H, m), 5.83–5.89 (1H, m), 5.90–5.96 (1H, m), 7.10–7.52 (10H, m). ^{13}C NMR (125 MHz, DMSO-d_6, 373K) δ 37.3, 42.4, 51.2, 66.6, 67.0, 123.2, 126.3, 126.8, 126.8, 127.3, 127.4, 127.76, 127.81, 135.6, 135.8, 154.1, 154.2, 170.4. HRMS (ESI) calcd for $C_{22}H_{21}O_6N_2$ 409.1405 $[M–H]^–$, found 409.1405.

(±)-*β*-Lysine (1) from 7: Platinum oxide (24.6 mg, 108 μmol) was added to a solution of **7** (151 mg, 368 μmol) in AcOH (3.8 mL). The atmosphere in the reaction vessel was then replaced with H_2 (1 atm). After stirred for 4 days under H_2, the reaction mixture was filtrated through Celite (10 cm^3, MeOH: 50 mL) and concentrated. The residue was dissolved in H_2O (5 mL), desalted twice with ion exchange resin column (DOWEX 50W-X4 100-200 mesh, 2 M NH_3 aq. for the first desalination, 1 M NH_3 aq. for the second) and concentrated in *vacuo* to afford **1** (49.8 mg, 341 μmol, 93%) as a pale yellow amorphous solid.

Dibenzyl 3-(2-ethoxy-2-oxoethyl)-3,6-dihydropyridazine-1,2-dicarboxylate (8): Dibenzyl azodicarboxylate (**3**) (1.7 M in CH_2Cl_2, 19 mL, 32 mmol) was added to a solution of ethyl (*E*)-hexa-3,5-dienoate (**6**) (4.08 g, 29.1 mmol) in toluene (73 mL) at 0 °C. The solution was warmed to room temperature, and stirred for 21 h. Then the reaction mixture was concentrated, and the residue was purified by flash column chromatography on silica gel (200 g, EtOAc/hexane 1/4 to 1/3) to afford **8** (12.0 g, 27.3 mmol, 94%) as a colorless oil: IR (neat) ν 2982, 1708, 1267, 1212, 1064, 752, 732, 695 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6, 373K) δ 1.12 (3H, br t, *J* = 6.3 Hz), 2.51–2.64 (2H, m), 3.76 (1H, br d, *J* = 17.2 Hz), 3.90–4.11 (2H, m), 4.27–4.34 (1H, m), 4.95–5.02 (1H, m), 5.05–5.22 (4H, m), 5.84–5.93 (2H, m), 7.10–7.51 (10H, m). ^{13}C NMR (125 MHz, DMSO-d_6, 373K) δ 13.3, 37.1, 42.3, 51.1, 59.4, 66.6, 67.0, 123.4, 126.0, 126.80, 126.82, 127.3, 127.4, 127.7, 127.8, 135.6, 135.8, 154.1, 154.2, 169.0. HRMS (ESI) calcd for $C_{24}H_{26}O_6N_2Na$ 461.1683 $[M+Na]^+$, found 461.1679.

(±)-*β*-Lysine (1) from 8: Platinum oxide (471 mg, 2.07 mmol) was added to a solution of **8** (9.00 g, 20.5 mmol) in AcOH (200 mL). The atmosphere in the reaction vessel was then replaced with H_2 (1 atm). The resultant mixture was vigorously stirred for 5 days under H_2, and sonicated to break platinum clusters about every 12 h. After H_2O (200 mL) and conc. HCl aq. (34 mL) were added, the reaction mixture was heated to 60 °C, and vigorously stirred for 2 days at the same temperature. The resultant mixture was filtrated through Celite (100 cm^3, MeOH: 1 L) and concentrated in *vacuo*. The residue was dissolved in H_2O (15 mL), desalted twice with ion exchange resin column (DOWEX 50W-X4 100-200 mesh, 2 M NH_3 aq.) and concentrated to afford **1** (2.70 g, 18.5 mmol, 90%) as a pale yellow amorphous solid. IR (neat) ν 2926, 2862, 1547, 1384 cm^{-1}. ^1H NMR (500 MHz, D_2O) δ 1.28–1.57 (4H, m), 2.18 (1H, dd, *J* = 14.4, 7.9 Hz), 2.31 (1H, dd, *J* = 14.4, 5.9 Hz), 2.58–2.63 (2H, m), 3.04–3.11 (1H, m). ^{13}C NMR (125 MHz, D_2O) δ 31.1, 36.3, 43.4, 48.3, 51.0, 184.2. HRMS (ESI) calcd for $C_6H_{15}O_2N_2$ 147.1128 $[M+H]^+$, found 147.1128.

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